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Synthesis of 10-Hydroxy-2-decenoic Acid (Royal Jelly Acid) from the Butadiene Telomer

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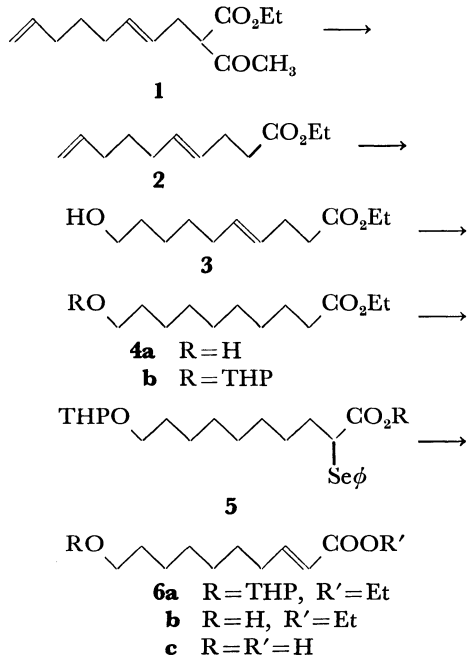
Synopsis. Ethyl 2-acetyl-4,9-decadienoate obtained by palladium catalyzed reaction of butadiene and ethyl acetoacetate was converted to 4,9-decadienoate. Hydroboration of the terminal olefin gave 10-hydroxy-4-decenoate. After hydrogenation and protection of the hydroxyl group, the double bond was created at the conjugated position by introduction of phenylseleno group and subsequent oxidative removal to give 10-hydroxyl-2-decenoic acid.

Royal jelly is a nutrient of queen bee *lavae*. Investigation of the lipids of royal jelly has revealed that their free acid fraction contained a complex mixture of C_{10} acids which are called royal jelly acids. The structure of the main component of the royal jelly acids was determined by Butenandt and Rembold as 10-hydroxy-2-decenoic acid.[1] Several synthetic methods for this physiologically interesting acid have been reported.[2] These syntheses are based on chain elongation of the shorter compounds *via* somewhat lengthy steps. We now wish to report a simple synthetic method for this acid starting from an easily available butadiene telomer which has the right carbon numbers and suitable functional groups for the synthesis of the acid.

Butadiene and ethyl acetoacetate react to give 2-acetyl-4,9-decadienoate (**1**)[3] in 80% yield (bp 91—93 °C/2 Torr) using palladium acetate and triphenylphosphine as a catalyst. It is apparent that this easily prepared compound has an ideal structure for the construction of the royal jelly acid, which was synthesized by the following sequences.



The acetyl group was removed by treatment of the ester **1** (63.5 g, 267 mmol) with sodium ethoxide in absolute ethanol (5.3 g, 78 mmol, 241 ml) to give, in 86% yield, ethyl 4,9-decadienoate **2**: bp 83 °C/1 Torr; NMR (CCl_4) δ 4.7—6.15 (m, 5H, olefin), 4.05 (q, J=7.0 Hz, 2H), 1.75—2.45 (m, 6H), 1.45—1.75 (m, 2H), 1.2 (t, J=7.0 Hz, 3H); IR (neat) 1735, 970, 910 cm^{-1}. Then the terminal double bond was converted to alcohol by hydroboration[4] using 1.1 equivalent of bis(1,2-dimethylpropyl)borane in dry THF and subsequent oxidation with 30% hydrogen peroxide in 3M sodium hydroxide solution to give, in 82% yield, 10-hydroxy-4-decenoate **3**: bp 118 °C/1 Torr; NMR (CCl_4) δ 5.3—5.6 (bt, 2H, olefin), 4.1 (q, J=7.0 Hz, 2H), 3.55 (bt, J=6.0 Hz, 2H), 3.2 (br, 1H, -OH), 2.3 (bs, 4H), 1.85—2.2 (br, 2H), 1.25 (t, J=7.0 Hz, 3H); IR (neat) 3600—3200, 1735, 975 cm^{-1}. The isomerization of the double bond at the position 4 of the ester **3** to the conjugated position would complete the synthesis. However, the attempted isomerization with various catalysts such as strong base, $RhCl(PPh_3)_3$, platinic acid, gave no clear result. Thus the double bond was hydrogenated by using palladium on carbon to give the saturated ester **4a** in 90% yield. The hydroxyl group was protected by converting to tetrahydropyranyl ether **4b** in 77% yield: NMR (CCl_4) δ 4.55 (br, 1H), 4.1 (q, J=7.0 Hz, 2H), 3.15—3.80 (m, 4H), 2.0—2.4 (m, 2H), 1.24 (t, J=7.0 Hz, 3H); IR (neat) 1738, 1040 cm^{-1}. Generation of the anion of saturated ester **4b** (900 mg, 3 mmol) with lithium isopropylcyclohexylamide (3.6 mmol) in dry THF at −78 °C was followed by the reaction of phenylselenenyl bromide[5] (991 mg, 4.2 mmol) to give, in 47% yield after column chromatography, the selenide **5**: NMR (CCl_4) δ 7.0—7.6 (m, 5H, phenyl), 4.4 (br, 1H), 3.95 (q, J=7.0 Hz, 2H), 3.2—3.7 (m, 5H), 1.12 (t, J=7.0 Hz, 3H). The purified selenide **5** (636 mg, 1.4 mmol) was oxidized with sodium periodate[5] (899 mg, 4.2 mmol) in aqueous methanol to give, in 81% yield after column chromatography, the desired unsaturated ester **6a**: NMR (CCl_4) δ 6.83 (dt, J=15.6 and 6.0 Hz, 1H, olefin), 5.67 (d, J=15.6, 1H, olefin), 4.4 (br, 1H), 4.10 (q, J=7.0 Hz, 2H), 3.2—3.7 (m, 4H), 1.8—2.4 (br, 2H), 1.25 (t, J=7.0 Hz, 3H). The removal of tetrahydropyranyl ether from ester **6a** (337 mg, 1.1 mmol) with copper sulfate (400 mg) in a mixture of methanol (8 ml) and water (2 ml) under reflux gave quantitatively the ethyl ester of royal jelly acid **6b**: NMR (CCl_4) δ 6.83 (dt, J=15.8 and 6.0 Hz, 1H, olefin), 5.67 (d, J=15.6, 1H, olefin), 4.10 (q, J=7.0 Hz, 2H), 3.50 (dt, 2H), 1.8—2.4 (br, 3H), 1.25 (t, J=7.0 Hz, 3H); IR (neat) 3100—3600, 1720, 1650, 980 cm^{-1}. The coupling constants of 15.6 and 15.8 for the olefinic protons of **6a** and **6b**

support the trans configuration of the olefins. Hydrolysis of the ester with 10% potassium hydroxide in aqueous methanol produced the royal jelly acid **6c** which was identified by its melting point, 63—64 °C (reported 64—65 °C).[2a)]

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